STAKEHOLDERS MEETING: We Have Come a Long Way, (But the Baby is still Waiting)

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Disclosure

- I have no conflicts of interest
- The opinions expressed are mine and do not reflect those of the FDA

Acronyms

FD&C Act- 1938	Food, Drug and Cosmetic Act
FDAMA-1997	Food & Drug Administration Modernization Act- Introduces Pediatric Exclusivity
BPCA- 2002/2007/2012	Best Pharmaceuticals for Children Act- Exclusivity
FDAAA - 2007	Food & Drug Administration Amendments Act
FDASIA - 2012	Food and Drug Safety and Innovation Act
Pediatric Rule	The 1998 “Requirement” - by regulation Struck down in 2002 by Courts: FDA does not have authority
PeRC - 2007	Pediatric Review Committee established
PREA- 2003/2007/2012	Pediatric Research Equity Act – Requirement by law Gives FDA the Authority to require pediatric studies
PPSR	Proposed Pediatric Study Request
WR	Written Request
PSP	Pediatric Study Plan
PIP	Pediatric Investigation Plan

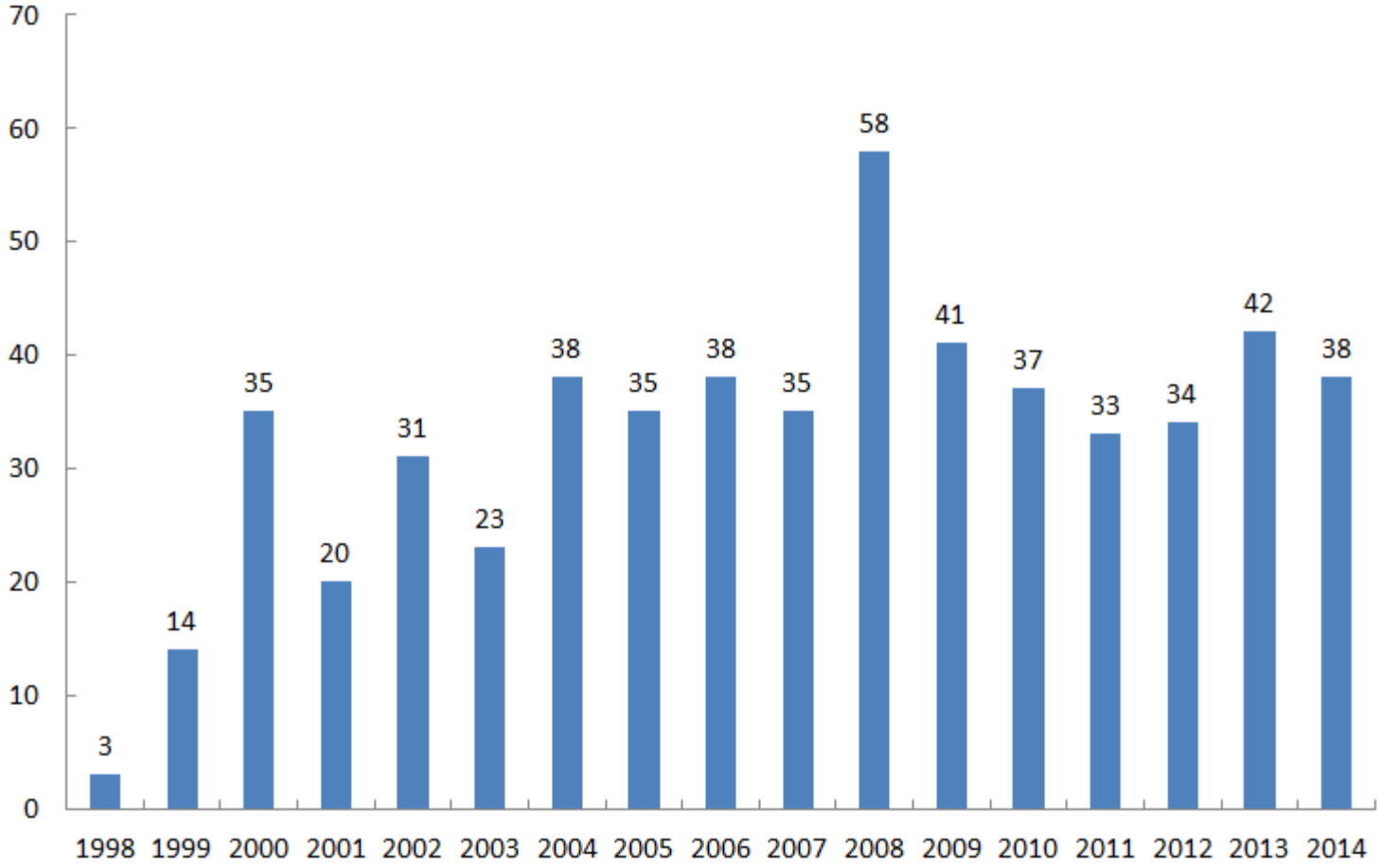
Historical Milestones and Legislation

- **1902** The Biologics Control Act enacted following the death of 22 children from tainted anti-toxins
- **1938** FD&C Act: Drugs must be Safe: enacted after 100 deaths, many in children, after use of Elixir Sulfanilamide
- **1962** Following thalidomide tragedy in Europe; Kefauver–Harris amendments require effectiveness
- **1962** The FD&C Act amended: Drugs not tested in children should not be used in children
- **1974** AAP Committee on Drugs issues guidelines for evaluating drugs for pediatric use
- **1977** AAP issues guidelines for ethical conduct in pediatric studies
- **1979** FDA requires sponsors to conduct pediatric clinical trials before including pediatric information in the labeling
- **1990** Institute of Medicine holds workshop regarding the lack of labeling for pediatric drugs
- **1992** Agency proposed Pediatric Labeling Rule and proposes extrapolation of efficacy from other data.
- **1994** Final Rule on Pediatric Labeling. Formalizes Extrapolation of Efficacy; manufacturers to update labeling if pediatric data existed; HOWEVER, it allowed a disclaimer to the labeling for drugs not evaluated in children
- **1994** Pediatric Plan to encourage voluntary development of pediatric data
- **1997** FDAMA creates pediatric exclusivity provision **(voluntary**), provides 6-month exclusivity incentive
- **1998** Pediatric Rule **(mandatory):** products are required to include pediatric assessments if the drug is likely to be used in a "substantial number of pediatric patients" (50,000) or if it may provide a "meaningful therapeutic benefit"
- **2002** Pediatric Rule declared invalid by DC Federal Court; the rule exceeded FDA's authority
- **2002** FDAMA reauthorized as BPCA. Maintains 6-month exclusivity added to patent life of the active moiety. Creates Office of Pediatric Therapeutics. Mandates pediatric focused safety reviews.
- **2003** PREA re-establishes many components of the FDA's 1998 pediatric rule. Orphan products are exempted
- **2007** FDAA Reauthorizes BPCA & PREA for 5 years : Pediatric Review Committee (PeRC) formed.
  Studies submitted will result in labeling. Negative and positive results of pediatric studies will be placed in Labeling.
- **2012** FDASIA legislation makes **permanent** BPCA and PREA

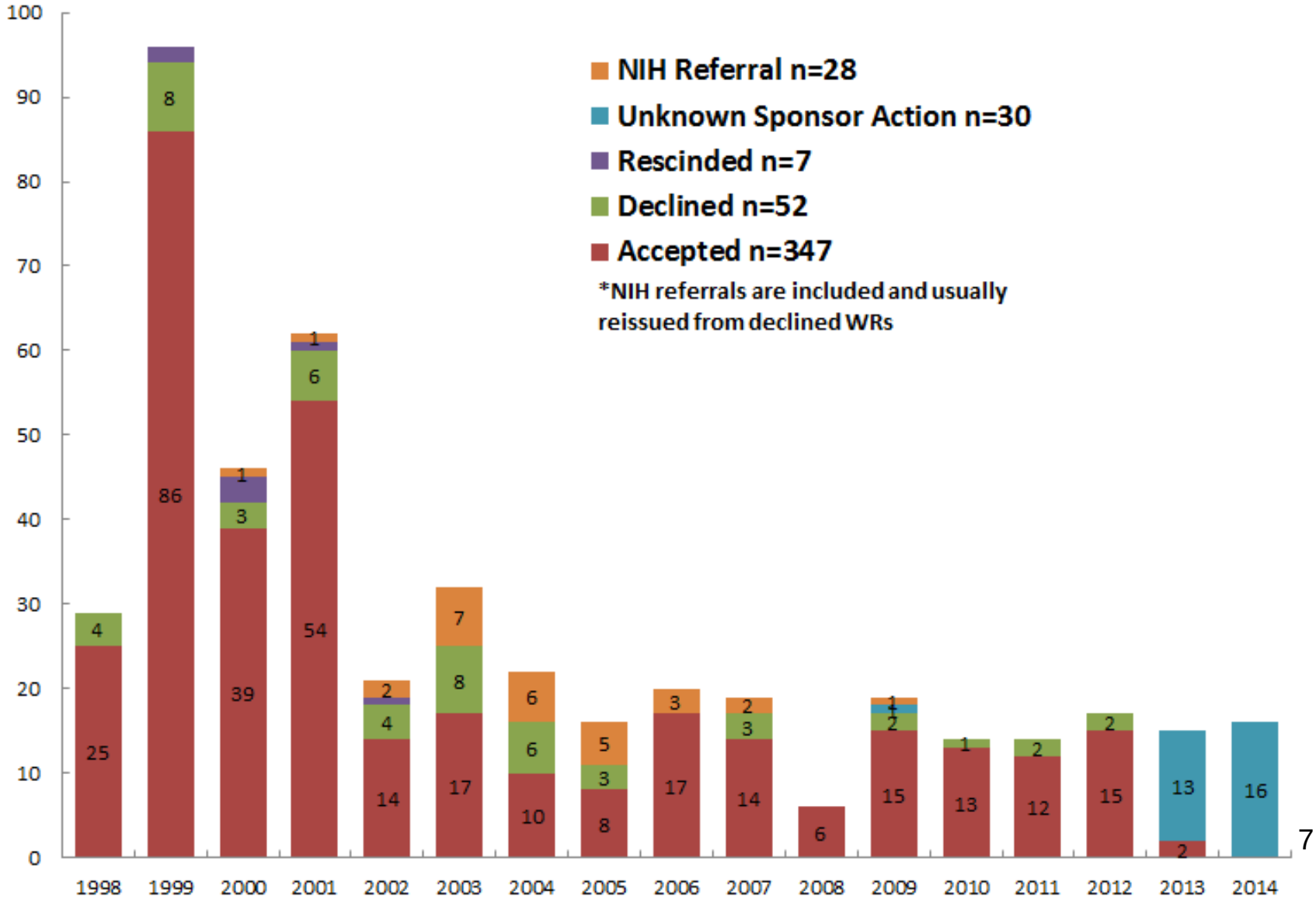
Overview of Accomplishments:
FDA/Clinicians/NIH/Parents/Patients

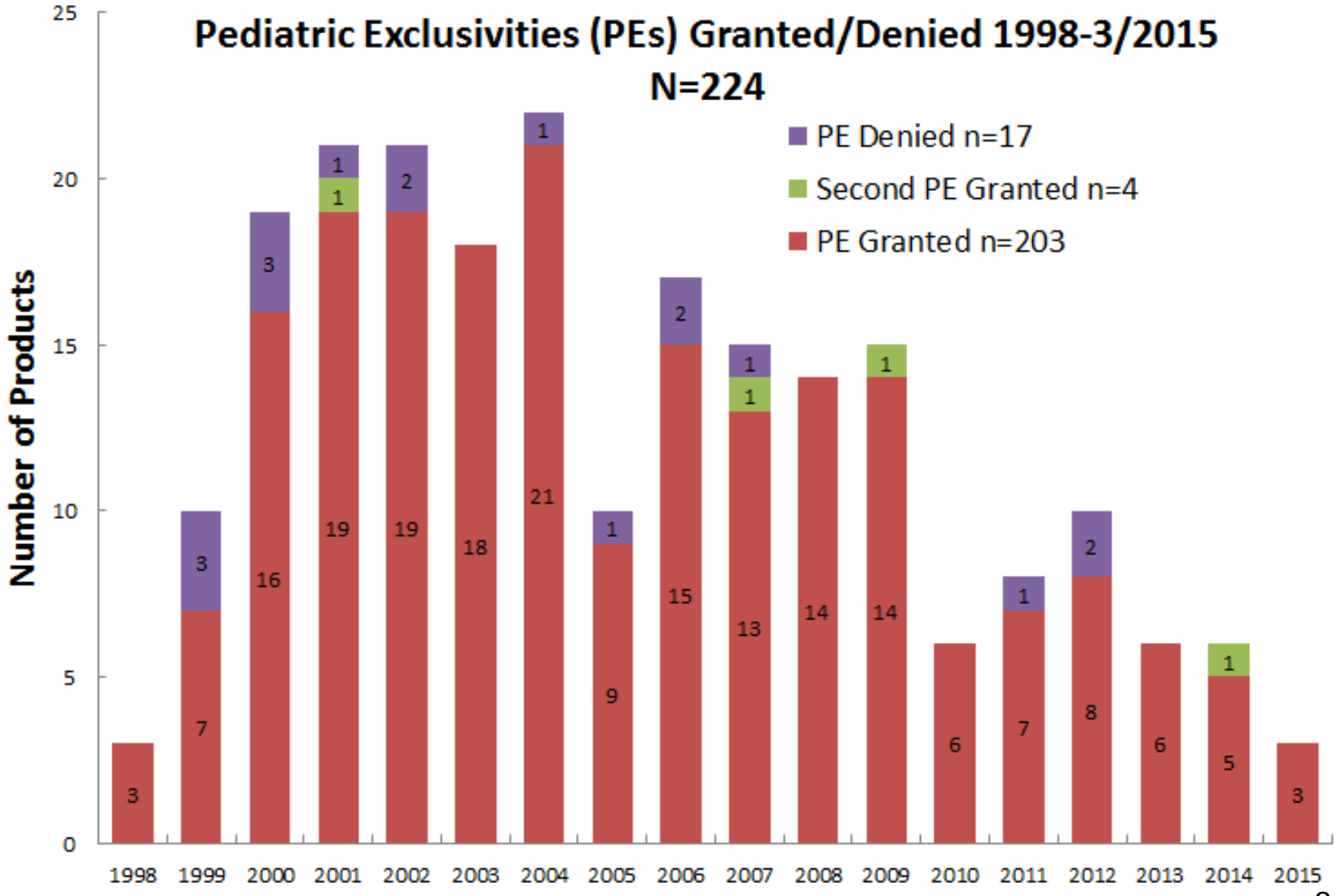
- **New Pediatric Labeling- March 18, 2015**
- N = **563:** BPCA only =163 PREA only = 274 BPCA/PREA =76 None=1 Peds Rule= 49
- **n = 513 with New Pediatric Studies;** n = 50 with No New Pediatric Studies
- N = **464 WR's issued** since 1998
  - 224 Exclusivity Determinations
  - 204 Approved Drugs Granted Exclusivity
- **Numerous publications on pediatric studies**

Number of Pediatric Labeling Changes 1998-2014 N=555



Unique Written Requests* Issued 1998-2014 N=464




Pediatric Exclusivities (PEs) Granted/Denied 1998-3/2015
N=224
PE Denied n=17
Second PE Granted n=4
PE Granted n=203
Number of Products
0
5
10
15
20
25
1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015
3
7 3
16 3
19 1 1
19 2
18
21 1
9 1
15 2
13 1 1
14
14 1
6
7 1
8 2
6
5 1
3

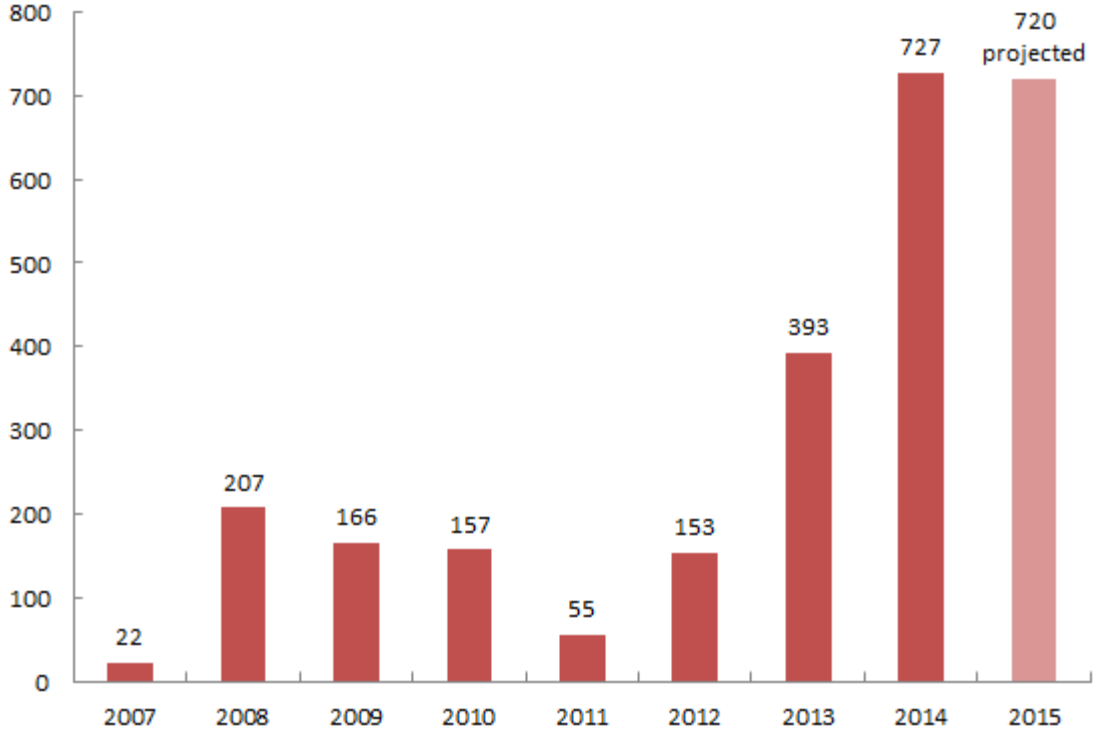
Pediatric Review Committee (PeRC)

- Established by FDASIA in 2007
- Effort to bring consistency in regulatory advice to a complex pediatric program
- Meets every Wednesday for 3 hours
- Volume of products per meeting has more than doubled in past two years
- Since August of 2012: over 1,200 indications and 650 unique molecules
- Over 700 Deferred PREA studies

Pediatric Review Committee (PeRC)

- Committee membership
  - Including staff from CDER, CBER, OC
  - Expertise in Pediatrics, Neonatology, Pediatric Ethics, Biopharmacology, Statistics, Chemistry, Law required
  - Appropriate expertise pertaining to the product under review
- Required to review items under PREA
  - All Pediatric Plans, Assessments, Deferrals, and Waivers
- Required to review items under BPCA
  - All Written Requests and Amended Written Requests prior to being issued

Number of Products Discussed at PeRC 2007-2015



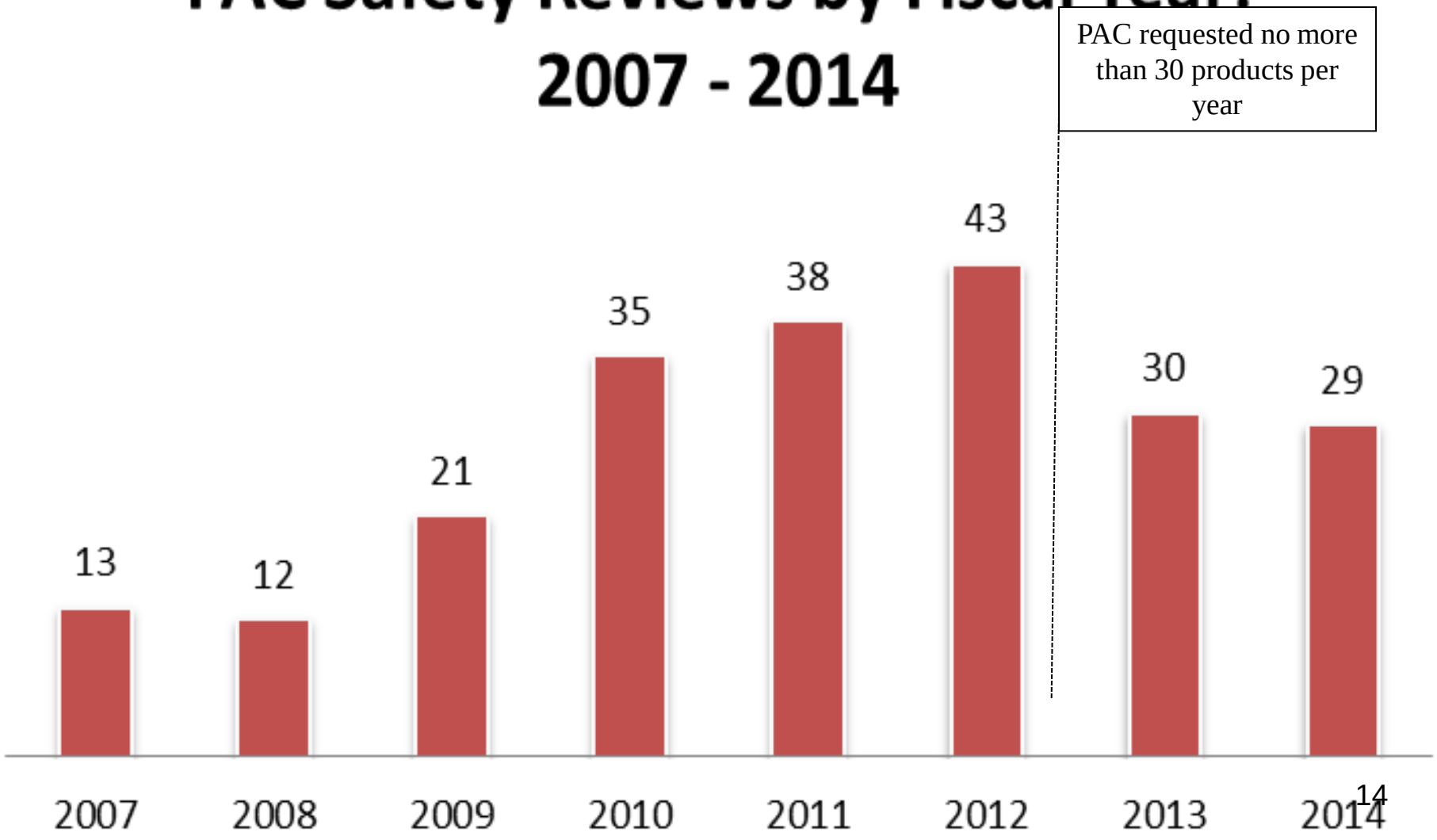
NIH and Pediatric Product Development

- Under BPCA, NIH administers a program to develop products that sponsors do not wish to develop for pediatrics
- Two products have been labeled via this mechanism and a dozen more are in the "submission pipeline"
  - Mostly for "off-patent" products but FDA can issue a Written Request for an "on-patent" product and if it is rejected, choose to send it to NIH
  - NIH can also send FDA a PPSR
- The NIH submission process is unique
  - The process includes public access to all data submitted
  - It requires the sponsor to "come to the table" and negotiate new pediatric labeling from the studies

Pediatric Safety Issues

- Mandated Pediatric Advisory Committee post marketing review of all products studied under WR's (2002), PREA (2007) and HDE's (2007)
- Office of Surveillance and Epidemiology targeted reviews of pediatric issues: *medication errors, excipients in neonates, metabolic syndrome in children, ADHD adverse effects, testosterone exposure from topical application in adults*
- Datamining increasingly being incorporated into the standard post marketing reviews.

PAC Safety Reviews by Fiscal Year: 2007 - 2014



International Implications

- US passed legislation and regulation in 1997 & 1998. Legal setback in 2002 on the Requirement resulted in 2003 PREA legislation that did not require pediatric studies until the adult studies were being submitted.

- In 2007 the Europeans passed legislation that required thinking of how the product might be used in pediatrics early, after Phase 1, in the adult development program.

- They had a strong requirement: 1) they can refuse to file the adult application if there is no pediatric investigational plan (PIP),
  2) Planning for pediatric studies should begin after Phase 1

- US 2012 Legislation modified PREA to push pediatric product development to earlier (Phase 2) in the adult development

International Product Development

- Ethically, children should not enter a trial unless it is going to provide some benefit and answer a question needed to achieve that benefit.

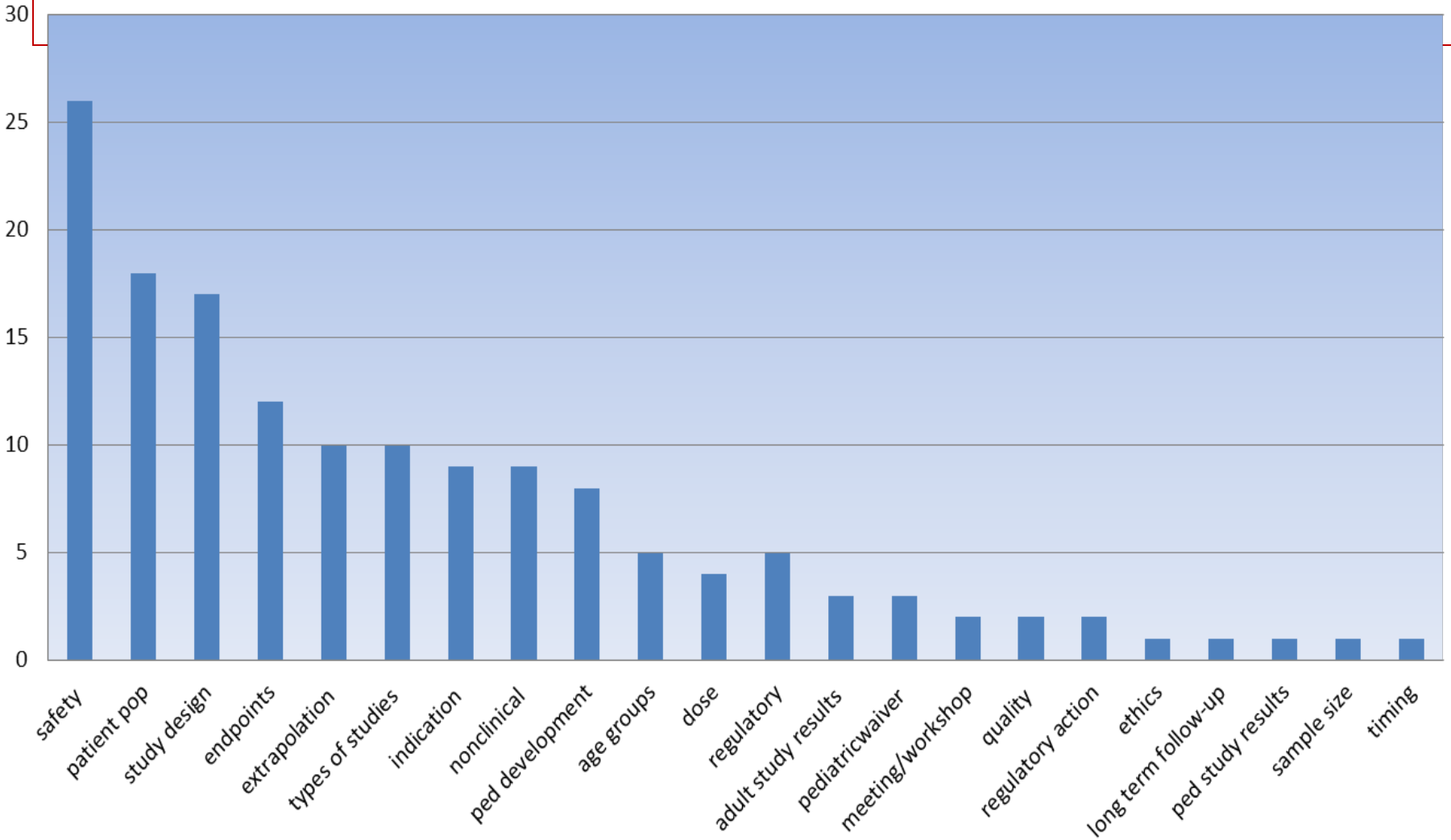
- The FDA and EMA determined we must coordinate pediatric product development for many reasons: ethical; limited numbers of children for studies requires many centers and nations; coordination of science

- Every month FDA/EMA and 3 other countries review pediatric trials that have ethical, scientific or safety issues.

European Networks

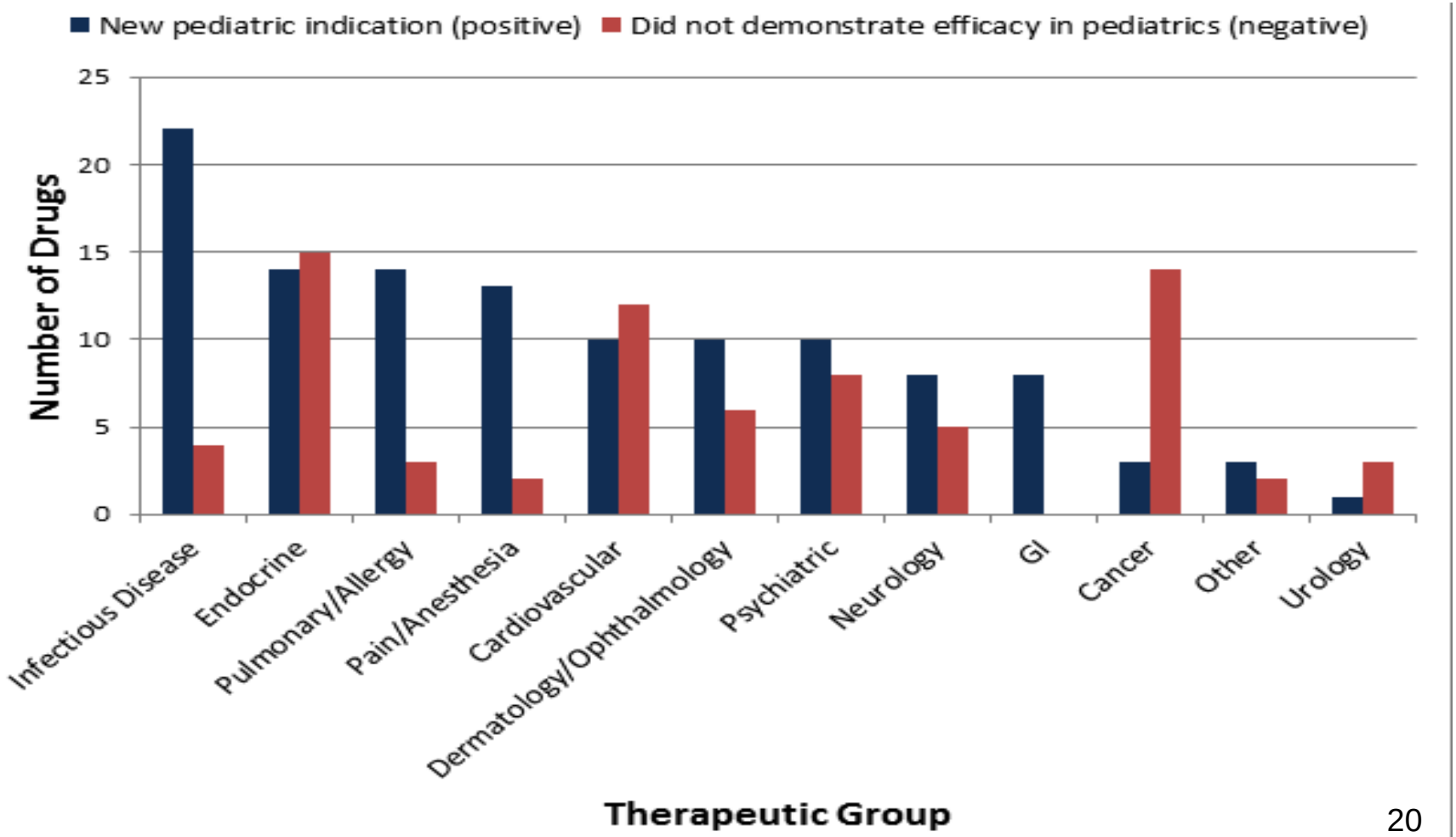
- Mandated by their legislation
- Funded by the European Commission
- Example of one which has solved most of the logistic questions is England's Medicines for Children Research Network
- The small numbers involved with pediatric diseases requires international cooperation and we need to be able to participate effectively

Of 400 Issues Discussed at Pediatric Cluster: n=150 Clinical Trial Issues



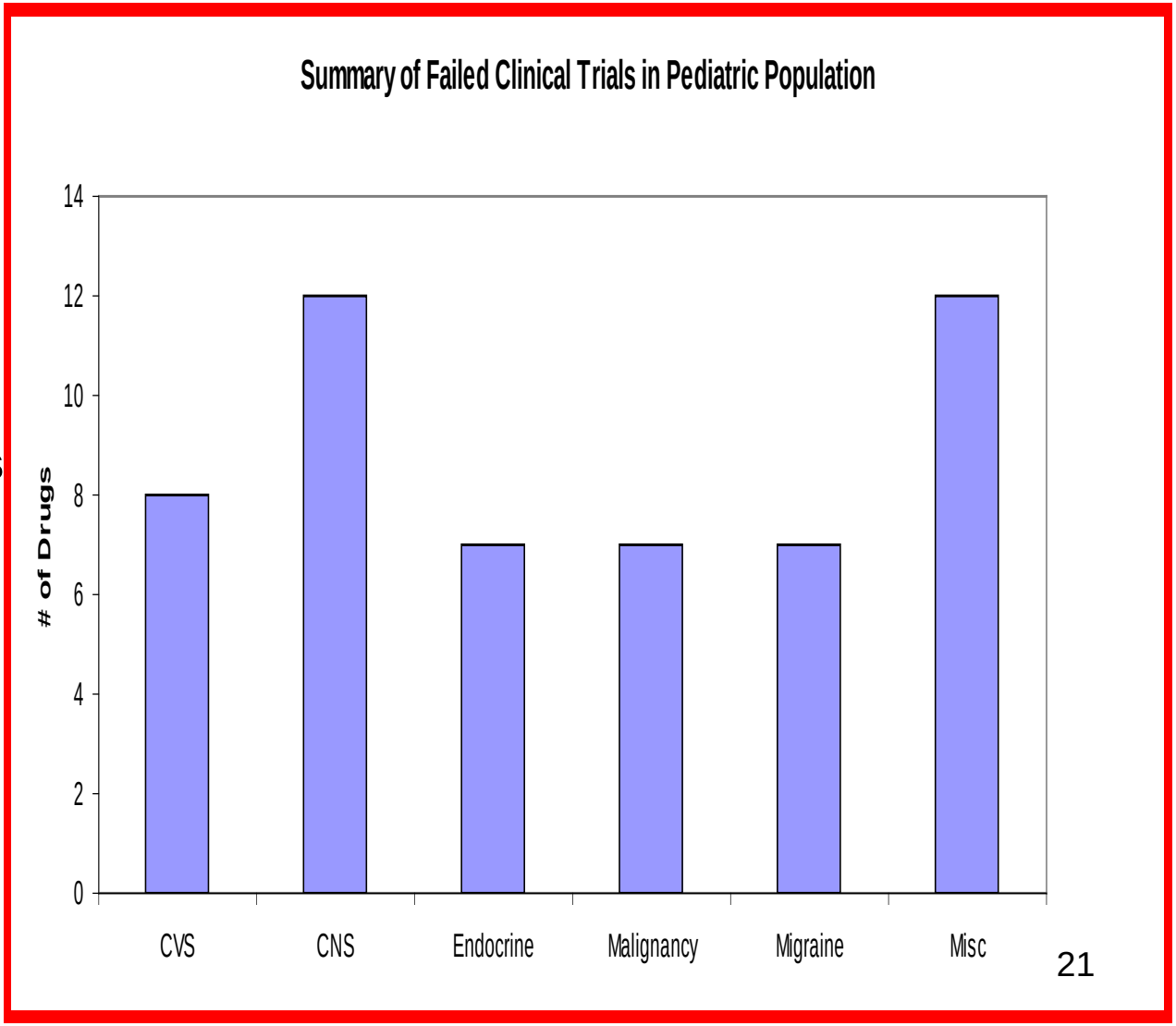
Though we are making progress, still a long way to go.

Overview of Pediatric Efficacy Trial Outcomes
(BPCA 1998-2012, n=190)



Cluster Distribution of Failed Pediatric Trials

- Cardiovascular system diseases
- Central nervous system diseases
- Endocrine diseases
- Malignancy
- Migraine
- Other diseases.



Factors Contributing to Failed Pediatric Trials

- **Trial design issue: high placebo effect; high drop-out**
- **Study endpoint issue: alternate endpoint**
- **Inappropriate patient selection**
- **Insufficient sample size and Failure to enroll**
- **Poor dose selection**
- **Differences in PK**

Conclusions

- Pediatric medical community should insist on incorporation of evidence based treatment sufficient to support pediatric product labeling
  - Journal publication and expert opinion are not sufficient
  - Is not the sole responsibility of FDA or drug product developers
- Seek commitment of the entire pediatric community to address this issue
  - Academic researchers and community practitioners
  - Patients and patient organizations
  - Professional Societies - Allied health care providers
- Develop Global Pediatric networks to conduct pediatric clinical trials that will meet regulatory standards
- Advance the science for neonates, oncology and rare diseases to better inform pediatric trials.

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Pediatrics

- New Pediatric Labeling Information Database
- **Safety Reporting Updates**
- **Pediatric Study Characteristics Database**
- **List of Exclusivity Determinations (PDF - 179KB)**
- **Medical, Statistical, and Pharmacology Reviews 7/9/2012- present**
- Medical, Statistical and Pharmacology Reviews 9/2007- 7/2012

Spotlight

- Gaucher disease - A Strategic Collaborative Approach from EMA and FDA
- Public Workshop – Pediatric Clinical Investigator Training
- 2014 Meeting Materials, Pediatric Advisory Committee to the FDA
- AAP News FDA Update
- FDA Pediatric Safety Communications

About Us

- Office of Pediatric Therapeutics


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